are presented in Table 1. Despite the fact that these values do not coincide in absolute value with one another (which may also be associated with the different geometries of the devices used), the character of their change on passing from one series of stereoisomers to another is retained. In fact, the $J_{[M-CH_3]^+}/J_{[M]^+}$ values also remain considerably higher in the case of Ia-IIIa, which contain an axial 2-CH_3 group, whereas the $J_{[M-R']^+}/J_{[M]^+}$ values for Ic-IIIc, with an axial 4-R' group, also remain higher than the values observed for their stereoisomers. It should be noted that no appreciable increase in the peaks of the dehydration ions was observed in the mass spectra obtained in the case of gas-chromatographic introduction.

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INDOLIZINES

IV.* PROTONATION OF 2-ALKYL(ARYL)-6- AND -7-CARBETHOXYINDOLIZINES AND THEIR FORMYL, ACETYL, AND NITROSO DERIVATIVES

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UDC 547.759.4.07:543.422.25

It was established by PMR spectroscopy that 2-alkyl(aryl)-6- and -7-carbethoxyindolizines are protonated at C_3, whereas their 3-formyl, 3-acetyl, and 3-nitroso derivatives are protonated at the oxygen atom of the substituent in the 3 position. The ionization constants of 24 indolizine derivatives in nitromethane relative to diphenylguanidine were measured by potentiometric titration. A correlation between protonation and electrophilic substitution in the 2-alkyl(aryl)-6- and -7-carbethoxyindolizine series was established.

In preceding communications of this series [1-3] we described the syntheses of 2-alkyl(aryl)-6- and -7-carbethoxyindolizines and their transformations under the influence of electrophilic and nucleophilic agents. In the present research we studied the protonation of 2-alkyl(aryl)-6- and -7-carbethoxyindolizines (I, V) and their formyl (II, VI), acetyl (III, VII), and nitroso (IV, VIII) derivatives, and the results were compared with the results of previously investigated transformations of these compounds under the influence of other electrophilic reagents.

The protonation centers of the investigated compounds were established on the basis of a study of the PMR spectra of the neutral molecules and conjugate acids (Table 1). In the spectra of neutral molecules the references of proton signals by the pyridine fragment are due to the character of their multiplicity. As in the case of 7-carbethoxyindolizines V-VIII, the proton in position 6 appears in the form of a quartet ($J_{5,6}$ = 7.5 Hz, $J_{6,8}$ = 1.8 Hz) in the region δ 6.90-7.20 ppm. The quartet of the proton at C_8 ($J_{5,8}$ = 0.9 Hz, $J_{6,8}$ = 1.8 Hz) is

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*See [1] for communication III.

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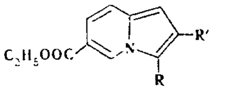
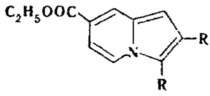
observed in the interval 7.95-8.30 ppm, while a proton signal at C_5 appears as a doublet ($J_{5,6}$ = 7.5 Hz), the components of which are further split ($J_{5,8}$ = 0.9 Hz and $J_{1,5}$ = 0.9 Hz) and have the form of a triplet. The chemical shifts of these signals depend significantly on the existence of a substituent in the peri position: in C_3-unsubstituted compound V the signal is found in the interval 7.66-7.85 ppm. In substances VI-VIII, having magnetic anisotropic groups (CHO, $COCH_3$, NO) at C_3, it is shifted to a weak field (9.63-10.25 ppm).

In the spectra of neutral molecule 6-carbethoxyindolizine I, a proton signal at C_5 appears in the form of an octet ($J_{5,8}$ = 1.05 Hz, $J_{5,7}$ = 1.5 Hz, $J_{1,5}$ = 0.75 Hz), which under the influence of ortho-carbethoxy groups is shifted to weaker field (8.60-9.60 ppm) when compared to the signals of the proton at C_5 in 7-carbethoxyindolizine V. Introduction of CHO, $COCH_3$, or NO groups into position 3 of 6-carbethoxyindolizines is accompanied by a shift of the proton signal at C_5 to a region of weak fields (10.33-10.68 ppm) for compounds II-IV. The protons at C_7 and C_8 in the spectra of 6-carbethoxyindolizines characterize systems of signals of type AB ($J_{7,8}$ = 9.0 Hz), the components of which are further split with $J_{5,7}$ = 1.5 Hz and $J_{5,8}$ = 1.05 Hz. Reference signals of protons of the pyrrole fragment follow from a comparison of the spectra of 1,3-unsubstituted and 3-substituted compounds (Table 1).


I-IV


V-VIII

I. V a R=H, R′=CH_3; b R=C_6H_5; c R=$C_6H_4CH_3$-*p*; d R=$C_6H_4OCH_3$-*p*; f R=C_6H_4Cl-*p*; g R=$C_6H_4NO_2$-*p*; II, VI a R=CHO, R′=CH_3; b R=C_6H_5; c R=$C_6H_4CH_3$-*p*; III, VII a R=$COCH_3$, R′=CH_3; b R=C_6H_5; c R=$C_6H_4CH_3$-*p*; IV, VIII a R=NO, R′=CH_3; b R=C_6H_5; c R=$C_6H_4CH_3$-*p*

An examination of the PMR spectra of C_1- and C_3-unsubstituted carbethoxyindolizine cations shows that protonation of these substances (I, V) occurs at the C_3 carbon atom, regardless of the position of the ester group in the pyridine portion of the molecule.

TABLE 1. Chemical Shifts in the PMR Spectra of the Neutral Molecules and Cations of 2-Alkyl(aryl)-6- and -7-carbethoxyindolizines*

Compound	Solvent	Proton signals, δ				
		1	3	5	6(7)	8
Ia	$CDCl_3$	6,22 bs	†	8,60 m	†	†
	CF_3COOH	6,97 bs	5,53 (2H)	9,55 m	8,97 q	8,02 q
Ib	$CDCl_3$	6,72 bs	†	8,68 m	†	†
	CF_3COOH	†	6,05 (2H)	9,60 m	8,98 q	8,08 q
Ig	CF_3COOH	7,75 bs	6,17 (2H)	9,70 m	9,08 q	8,23 q
IIa	$CDCl_3$	6,35 bs	9,87 s	10,33 m	7,70 q	7,38
	CF_3COOH	6,93 bs	8,60 s	10,33 m	8,60 q	7,90 q
IIb	$CDCl_3$	6,63 d	9,83 s	10,48 m	7,77 q	†
	CF_3COOH	7,17	8,67 s	10,38 m	8,63 q	8,02 q
IIIb	$CDCl_3$	6,50 d	2,05 s	10,63 m	7,69 q	7,44 q
	CF_3COOH	7,12	2,45 s	10,53 m	8,58 q	7,98 q
IVb	$CDCl_3$	6,97 d	—	10,82 m	8,11 q	7,62 q
	CF_3COOH	†	—	10,68 m	9,09 q	7,62 q
Va	CCl_4	6,38 bs	7,09 q	7,66 dt	6,90 q	7,95 bq
	$CDCl_3$	6,48 bs	†	7,78 dt	6.97 q	8,03 bq
	CF_3COOH	6,97	5,53 (2H)	9,03 bs	8,27 q	8,50 bq
Vb	$CDCl_3$	6,95 bs	†	7,85 dt	7,03 q	8,15 bq
	CF_3COOH	7,50 bs	6,03 (2H)	9,10 bs	8,30 q	8,60 bq
Vg	CF_3COOH	7,78 bs	8,15 (2H)	9,23 bs	8,43 q	8,75 bq
VIa	CCl_4	6,38 bs	9,80 s	9,53 dt	7,23 q	7,98 q
	$CDCl_3$	6,52 bs	9,90 s	9,65 dt	7,35 q	8,13 q
	CF_3COOH	6,98 bs	8,63 s	9,67 bs	8,05 q	8,50 q
VIb	$CDCl_3$	6,82 d	9,83 s	9,78 dt	†	8,28 q
	CF_3COOH	7,25	8,70 s	9,80 dt	8.12 q	8,60 q
VIIb	$CDCl_3$	6,67 d	2,05 s	9,93 dt	†	8,23 q
	CF_3COOH	7,18	2,43 s	9,91 dt	8,08 q	8,57 q
VIIIb	$CDCl_3$	7,07	—	10,25 dt	7,61 q	8,30 q
	CF_3COOH	†	—	10,21 dt	8.40 q	8.62 q

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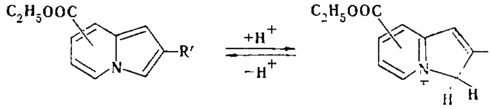
*Abbreviations: s is singlet, bs is broad signal, d is doublet, q is quartet, dt is doublet of triplets, bq is broad quartet, and m is multiplet.

†The signals are found in the region of phenyl ring protons.



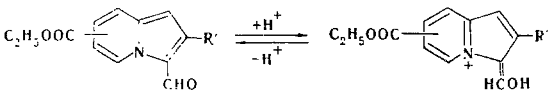
A signal with an intensity of 2 proton units, which was assigned to the protons of the methylene group in the 3 position, is observed in the spectra of the cations of compounds of this type at 5.50-6.00 ppm. The signal of the methylidyne proton attached to C_1 is shifted to weak field relative to the spectrum of the neutral molecule and appears at 6.97-7.50 ppm. A similar position of the signals is also observed in the case of other α-protonated alkylindolizines [4]. The signals of the protons of the pyridine portion of the molecules are shifted to the weak-field region ($J_{5,8}$ = 0.43-1.27 Hz) without a change in their multiplicity on passing from neutral I and V to their cations.

The results constitute evidence for a change in the ambident properties of the indolizine system when an ester group is introduced into the pyridine portion of the molecule (in the 6 or 7 position). It has been previously shown [5] that 2-phenylindolizine at −15° in CF_3COOH generates two isomeric forms (α and β) of the conjugate acid, which correspond to the addition of a proton to the C_3 and C_1 atoms, during which the percentage of the β form reaches 40%. The production of the β form was not observed when the protonation of isomeric 2-phenyl-6- and -7-carbethoxyindolizines was carried out under the same conditions. The only product of protonation of I and V was the α form of the conjugate acid.

The introduction of CHO, $COCH_3$, or NO groups in the 3 position of the investigated compounds leads to a change in the protonation center.

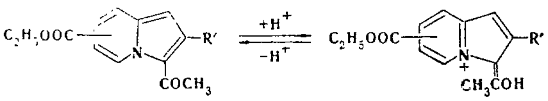
Signals of protons at 4.10-6.10 ppm are absent in the PMR spectra of the conjugate acids of the 3-formyl (II, VI), 3-acetyl (III, VII), and 3-nitroso derivatives (IV, VIII) (Table 1 and Fig. 1), and this excludes the C_1 and C_3 atoms as proton-addition centers.

In addition, on passing from the neutral molecules to the conjugate acids (for example, in the case of 3-formyl-substituted II and VI), the signal of the proton of the substituent in the 3 position is shifted to strong field by 1.10-1.30 ppm. These data constitute evidence that the structure of the conjugate acid for II and IV corresponds to the addition of a proton to the oxygen atom of the CHO group (Fig. 1).



The signals of the protons attached to C_1, $C_{6(7)}$, and C_8 in II and VI are shifted to weak field on passing from the neutral molecules to the cations, and the chemical shift remains practically unchanged only for the proton attached to C_5 (Table 1); this is evidently associated with compensation of the weak-field shift of the signal of this proton by the corresponding strong-field shift under the influence of a change in the magnetic anisotropy of the substituent in the 3 position of the protonated molecules. The change in the chemical shifts of the signals of the protons of the acetyl group is relatively small in the protonation of 3-acetylindolizines III and VII. However, the complete analogy in the spectra of the conjugate acids of 3-acetyl- (III, VII) and 3-formylindolizine derivatives (II, VI) provides evidence for protonation of these compounds at the carbonyl oxygen atom.

The results are in agreement with the data on the structure of the conjugate acids of acetylpyrroles [6], which add a proton to the same center.



The characteristic changes in the chemical shifts of the signals of the protons of the pyridine portion of the molecule displayed during protonation of 3-formyl- and 3-acetylcarbethoxyindolizines II, III, VI, and VII are also observed in the case of the cations of the corresponding 3-nitroso derivatives (IV, VIII) (Table 1 and Fig. 1). This makes it possible to conclude that the structure of the cations of IV and VIII corresponds to the addition of a proton to the oxygen atom of the nitroso group:

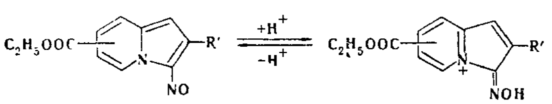


TABLE 2. ΔpK_a Values of 2-Alkyl(aryl)-6- and -7-carbethoxyindolizines

6-Carbethoxyindolizines	ΔpK_a	7-Carbethoxyindolizines	ΔpK_a
Ia	7,76	Va	8,84
Ib	9,00	Vb	9,95
Ic	8,30	Vc	9,20
Id	7,75	Vd	9,10
Ie	9,29	Vf	10,06
Ig	10,46	Vg	11,00
IIb	>11	VIb	>11
IIc	>11	VIc	>11
IIIb	>11	VIIa	>11
IIIc	>11	VIIb	>11
IVa	5,97	VIIIb	7,02
IVb	6,75		
IVc	5,75		

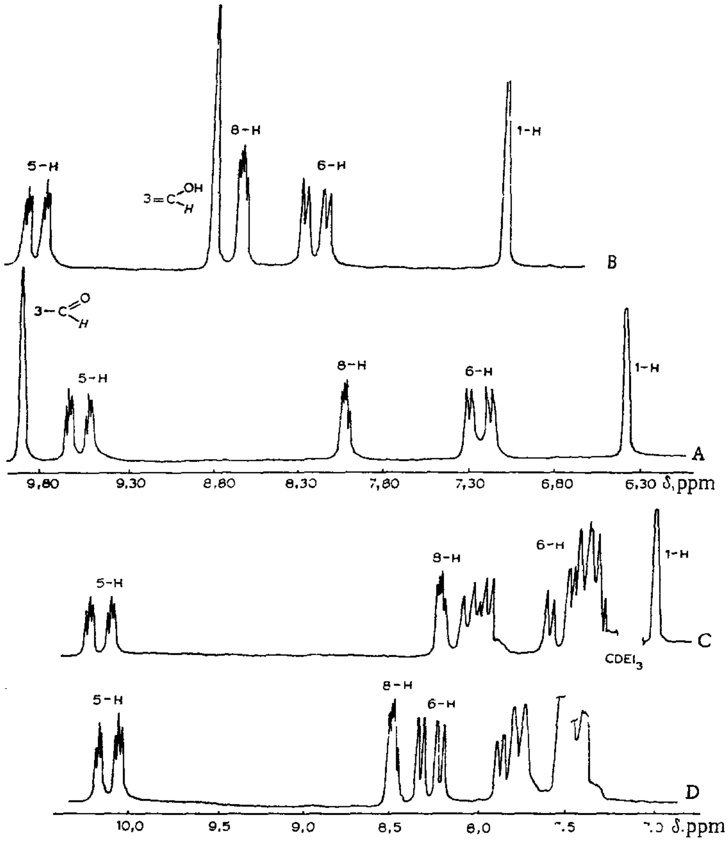


Fig. 1. PMR spectra of the neutral molecules and cations of 3-formyl- (VIa) and 3-nitroso-7-carbethoxyindolizine (VIIIb): A) VIa in CCl_4; B) VIa in CF_3COOH; C) VIIIb in $CDCl_3$; D) VIIIb in CF_3COOH.

The spectra of the cations of all of the investigated compounds remain unchanged with time, and this constitutes evidence for the thermodynamic stability of the protonated forms.

The basicities of the 2-alkyl(aryl-6- and -7-carbethoxyindolizines and their formyl, acetyl, and nitroso derivatives were quantitatively evaluated by potentiometric titration. The differences in the pH values at the half-neutralization points of nitromethane solutions of a standard substance (diphenylguanidine) and 24 indolizine compounds I-VIII were determined. The values found, designated as ΔpK_a, are a measure of the basicities of the compounds and are presented in Table 2.

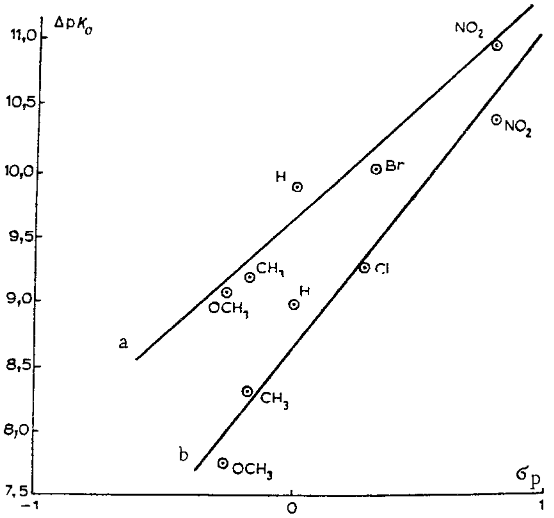


Fig. 2. Dependence of the ΔpK_a values of 2-(p-substituted phenyl)-6- and -7-carbethoxyindolizines on the Hammett σ_p values: a) for the 7-carbethoxy series; b) for the 6-carbethoxy series (the values of the para substituents in the phenyl ring attached to C_2 of the indolizine molecules are presented on the graph).

An analysis of the results provides evidence that the ΔpK_a values for C_3-unsubstituted indolizine derivatives I and V depend to a considerable extent on the position of the carbethoxy group. All of the compounds of the 7-carbethoxy series (V), in which the ester residue is para-oriented to the protonation center, are characterized by higher ΔpK_a values and, consequently, by lower basicities than their 6-carbethoxy analogs, which contain an ester group in the meta position. Within the limits of each of the two series (6-carbethoxy and 7-carbethoxy derivatives), the effect of para substituents in the phenyl ring attached to C_2 is satisfactorily described by Hammett σ_p constants. The correlation dependence of ΔpKa on σ_p is graphically expressed by two straight lines (Fig. 2) and is described by Eqs. (1) and (2)

$$\Delta pK_a = 9.645 + 1.806\sigma_p \quad (r\ 0.981;\ s^2\ 0.03). \tag{1}$$

$$\Delta pK_a = 8.685 + 2.421\sigma_p \quad (r\ 0.997;\ s^2\ 0.06) \tag{2}$$

for the 7- and 6-carbethoxyindolizine derivatives, respectively.

Sharp changes in the ΔpK_a values (by several orders of magnitude) occur on passing from C_3-unsubstituted compounds to 3-formyl, 3-acetyl, or 3-nitroso derivatives in both series; this is in good agreement with the PMR spectral data on the change in the protonation center of the substances.

It should be noted that the peculiarities of the protonation of 6- and 7-carbethoxyindolizine derivatives presented in this paper correlate well with the previously described effect [1-3] on their reactivities of the position of the carbethoxy group in the pyridine fragment of the molecule. Thus, for example, the higher basicities of 6-carbethoxy-2-alkyl(aryl)indolizines as compared with their 7-carbethoxy isomers are in agreement with the higher reactivities of these compounds in acylation and nitrosation and in the Mannich and Vilsmeier reactions.

EXPERIMENTAL

The synthesis of the compounds was described in [1-3]. The PMR spectra of solutions of all of the investigated compounds (the solvents for the neutral forms were CCl_4 and $CDCl_3$, and the solvent for the protonated forms was CF_3COOH) were recorded with a JEOL C-60 spectrometer (60 MHz) with tetramethylsilane as the internal standard. Potentiometric titration was carried out with a Radiometer automatic apparatus (Denmark) with a glass-calomel electrode pair at 30° in nitromethane. A 0.1 N solution of perchloric acid in nitromethane was used as the titrating agent. The concentration of the free base in the titrated solution at the half-neutralization point was ~0.015 g-equivalent/liter. Diphenylguanidine was used as the standard substance in the determination of the ΔpK_a values.

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SYNTHESIS OF 1-PHENYL-3-METHYL-4-ALKYL-4-[N-METHYLBUTYRO(CAPRO)LACTYL]-5-PYRAZOLONES

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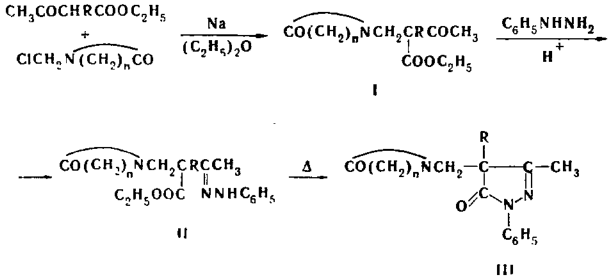
G. B. Ambartsumyan, and M. T. Dangyan

UDC 547.775.778.07

The corresponding hydrazones, which on heating are cyclized to give 1-phenyl-3-methyl-4-alkyl(benzyl)-4-(2-oxopyrrolidinomethyl)- and 1-phenyl-3-methyl-4-alkyl(benzyl)-4-(N-methylcaprolactyl)pyrazolones, are formed in the reaction of alkyl(benzyl)(2-oxopyrrolidinomethyl)- and alkyl(benzyl)(N-methylcaprolactyl)acetoacetic esters with phenylhydrazine.

5-Pyrazolones with lactam rings in the side chain are unknown. Since the lactam ring increases the complexing ability, the hydrophilic character, the dye affinity, the solubility, and the biological activity [1-6], a study of the reaction of phenylhydrazine with ethyl alkyl(benzyl) (2-oxopyrrolidinomethyl)- and alkyl(benzyl)(N-methylcaprolactyl)acetoacetates (Table 1) seemed of definite interest. The latter were obtained from N-(α-chloroalkyl)lactams, in view of the lability of their halogen atoms [6, 7]. Intense bands at 1733 (ester C=O), 1712 (ketone C=O), and 1692 cm^{-1} (lactam C=O) are observed in the IR spectra of these compounds.



I—III a n=3, R=C_4H_9; b n=3, R=C_5H_{11}; c n=3, R=$CH_2C_6H_5$; d n=5, R=C_4H_9; e n=5, R=C_5H_{11}; f n=5, R=$CH_2C_6H_5$

Esters I react with phenylhydrazine in an equimolar ratio at room temperature in the presence of one to two drops of glacial acetic acid to give corresponding hydrazones II. Their IR spectra contain characteristic

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Erevan State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1546-1548, November, 1976. Original article submitted November 24, 1975.